Notice of Allowability	Application No.	Applicant(s)	
	10/681,924	DHAR ET AL.	
	Examiner	Art Unit	
	Anthony J. Paviglianiti	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *original claims filed October 9, 2003*.

2. ☒ The allowed claim(s) is/are *1 - 20*, as amended. AJP

3. ☐ The drawings filed on _____ are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20050324* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

MC

DETAILED ACTION

Claims 1 – 20 are currently pending in the instant application and were subject to the following restriction. **Claims 19 – 20** were initially withdrawn pursuant to 37 C.F.R. §1.142(b) as being drawn to a non-elected invention; however, upon searching the art and finding certain product claims which were allowable, the restriction was expressly withdrawn by the examiner and the entire invention (i.e., **Claims 1 – 20**) was subsequently examined on the merits for patentability. An Examiner's Amendment follows the analysis below.

Priority

This application claims benefit of U.S. Provisional Application 60/417,935, filed on October 11, 2002.

Information Disclosure Statement

The Information Disclosure Statement filed on July 14, 2004, is in compliance with the provisions of 37 C.F.R. §1.97 and was considered by the examiner.

Election/Restrictions

Note: After preliminary examination of the elected invention, the following requirement for restriction was later withdrawn, as described below.

The Markush groups set forth in the claims include both independent and distinct inventions, and patentably distinct compounds (or species) within each invention. However, this application discloses and claims a plurality of patentably distinct inventions far too numerous to list individually. Moreover, each of these inventions contains a plurality of patentably distinct compounds, also far too numerous to list individually. **For these reasons provided below, restriction to one of the following inventions is required under 35 U.S.C. 121,** wherein an

Invention is a set of patentably distinct inventions of a broad statutory category (e.g., compounds, methods of use, methods of making, etc.):

I. **Claims 1 - 18**, drawn to compounds and compositions of formulas (I) and (Ia), as depicted in Claims 1 and 10, classified in classes 548, subclass 302.7; class 544, subclass 335, and other subclasses.

II. **Claims 19** and **20**, drawn to methods of using compounds of formula (I), acting as inhibitors of LFA-1/ICAM ("Lymphocyte Function-Associated Antigen 1/InterCellular Adhesion Molecule"), classified in class 514, subclasses 387, 252.06, and other subclasses.

In addition to an election of one of the above Groups, restriction is further required under 35 U.S.C. §121 as follows:

In accordance with the decisions in In re Harnisch, 631 F.2d 716, 206 USPQ 300 (CCPA 1980) and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App & Int. 1984), restriction of a Markush group is proper where the compounds with the group either (1) do not share a common utility, or (2) do not share a substantial structural feature disclosed as being essential to that utility. In addition, a Markush group may encompass a plurality of independent and distinct inventions where two or more members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. §103 with respect to the other member(s).

If **Groups I - II** are elected, **an election of a single compound is further required**, including an exact definition of each substitution on the base molecule [formula (I)], where a single member at each substituent group is selected. For example, if the base molecule has a

substituent group **Q–Ar**, where **Q** is recited to be "a bond, -C(=O)- or branched or straight chain C_{1-4} alkylene optionally substituted with one to two R_4," and **Ar** is recited to be any "optionally-substituted aryl or heteroaryl," then applicant must select a single value for Q, such as a methylene chain, and a single value for **Ar**, such as phenyl, and so on for each and specific values at each subsequent variable position, so that a single compound is identified.

One suggestion for the election of a single compound would be to select one of the compounds in Example 1 – Example 12 (Specification on pages 49 – 57).

In the instant case, upon election of a single compound, the Office will review the claims and disclosure to determine the scope of the independent invention encompassing the elected compound (compounds which are so similar as to be within the same inventive concept and reduction to practice). The scope of an independent invention will encompass all compounds within the scope of the claim which fall into the same class and subclass as the elected compound, but may also include additional compounds which fall in related subclasses.

Examination will then proceed on the elected compound *and* the entire scope of the invention encompassing the elected compound as defined by common classification. A clear statement of the examined invention, defined by those class(es) and subclass(es) will be set forth in the first action on the merits.

Note that the restriction requirement will not be made final until such time as Applicant is informed of the full scope of compounds along with (if appropriate) the process of using or making the compounds under investigation. This will be set forth by reference to specific class(es) and subclass(es) examined.

Should Applicant traverse on the ground that the compounds are not patentably distinct, Applicant should submit evidence or identify such evidence now of record showing the compounds to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. §103(a) of the other invention.

All compounds falling outside of the class(es) and subclass(es) of the selected compound and any other subclass encompassed by the election above will be directed to non-elected subject matter and will be withdrawn from consideration under 35 U.S.C. §121 and 37 C.F.R. §1.142(b). Applicant may reserve the right to file divisional applications on the remaining subject matter. The provisions of 35 U.S.C. §121 apply with regard to double patenting covering divisional applications.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. §1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 C.F.R. §1.48(b) and by the fee required under 37 C.F.R. §1.17(i).

If desired upon election of a single compound, applicants can review the claims and disclosure to determine the scope of the invention and can set forth a group of compounds which are so similar within the same inventive concept and reduction to practice. Markush claims must be provided with support in the disclosure for each member of the Markush group. See MPEP §608.01(p). Applicant should exercise caution in making a selection of a single member for each substituent group on the base molecule to be consistent with the written description.

Rationale Establishing Patentable Distinctiveness Within Each Group

Each Group listed above is directed to or involves the use of compounds which are recognized in the art as being distinct from one another because of their diverse chemical structure, their different chemical properties, modes of action, different effects and reactive conditions (MPEP §806.04, MPEP §808.01). Additionally, the level of skill in the art is not such that one invention would be obvious over the other invention (Group); i.e., they are patentable over each other. Chemical structures which are similar are presumed to function similarly, whereas chemical structures that are not similar are not presumed to function similarly. The presumption even for similar chemical structures though is not irrebuttable, but may be overcome by scientific reasoning or evidence showing that the structure of the prior art would not have been expected to function as the structure of the claimed invention. Note that in accordance with the holding of Application of Papesch, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and In re Lalu, 223 USPQ 1257 (Fed. Cir. 1984), chemical structures are patentably distinct where the structures are either not structurally similar, or the prior art fails to suggest a function of a claimed compound would have been expected from a similar structure.

The above Groups represent general areas wherein the inventions are independent and distinct, each from the other, because of the following reasons:

Group I and **Group II** are related as product and method of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially-different process of using that product. MPEP §806.05(h). Applying this rule to the instant case, the process for using the products can be

practiced with another materially-different product, as can be shown by reference in the Specification itself, where chemical compounds such as thiadiazole-amide derivatives (i.e., materially different than in the present invention) could be used as inhibitors of LFA-1/ICAM for use as anti-inflammatory agents. (See Specification at p. 3, lines 20 – 23).

In addition, because of the plethora of classes and subclasses in each of the Groups, a serious burden is imposed upon the examiner to perform a complete search of the defined areas. Therefore, for the reasons given above, the restriction set forth is proper, and not to restrict would impose a serious burden in the examination of this application.

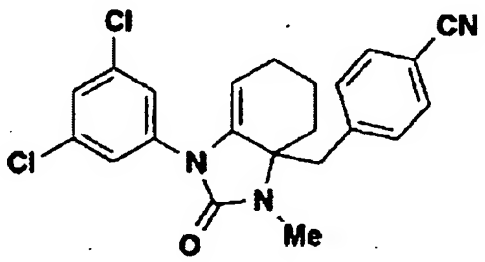
Advisory of Rejoinder

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Election by applicant

During a telephone conversation with Laurelee Duncan, Esq., on March 25, 2005, the above restriction requirements were discussed, and election without traverse was made by telephone of Group I, and the specific chemical compound of Example 3 on page 50 of the Specification, which is 4-[1-(3,5-Dichlorophenyl)-3-methyl-2-oxo-1,2,3,4,5,6-hexahydro-benzimidazol-3a-ylmethyl] benzonitrile, which has the



structure: . Applicant is advised that the reply to this requirement to be complete must include an election of the Invention to be examined even though the requirement be traversed. 37 C.F.R. §1.143.

Applicant is further advised that a reply to this requirement must include an identification of the specific compound that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Rejoinder of claims and withdrawal of restriction requirement

After examination of the elected chemical compounds and the expansion of the search to related compounds, it was determined that certain claimed compounds of the invention were free of the prior art and thereby directed to an allowable product. Therefore, consistent with the

"Advisory of Rejoinder," *supra*, **Claims 19 – 20 were rejoined** and will be examined for patentability under 37 C.F.R. §1.104.

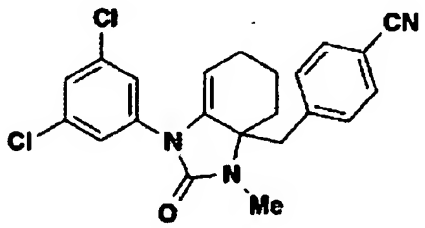
Since all claims previously withdrawn from consideration under 37 C.F.R. §1.142 have been rejoined, the restriction requirement made in this Office Action is hereby expressly withdrawn and all claims will be examined for patentability.

Analysis of Claims (Prior Art Searched)

The application was searched as follows:

Elected Compound:

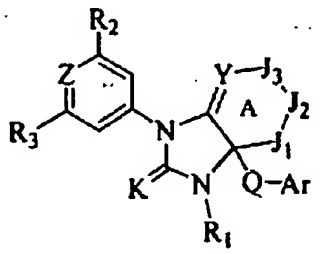
The elected compound of 4-[1-(3,5-Dichlorophenyl)-3-methyl-2-oxo-1,2,3,4,5,6-hexahydro-benzimidazol-3a-ylmethyl] benzonitrile, which has the



structure: , was searched and found to be free of the prior art.

Expansion of search to related compounds

The search of the prior art was expanded to related compounds within the same U.S. Patent classification as the elected compound. Upon finding no prior art, the scope of the search of prior art was expanded four additional times until it encompassed the following compounds of



formula (I), as depicted in **Claim 1**, wherein:

K is O or S;

Z is N or C($\mathbf{R^8}$);

Y is N or C($\mathbf{R^8}$);

$\mathbf{J_1}$ is N($\mathbf{R_5}$) or -C($\mathbf{R_{6a}R_{7a}}$)- [**note:** but $\mathbf{J_1}$ is *not* a bond];

$\mathbf{J_2}$ is N($\mathbf{R_5}$) or -C($\mathbf{R_{6b}R_{7b}}$)-;

$\mathbf{J_3}$ is N($\mathbf{R_5}$) or -C($\mathbf{R_{6c}R_{7c}}$)-; and only one of $\mathbf{J_1}$, $\mathbf{J_2}$ and $\mathbf{J_3}$ may be N$\mathbf{R_5}$ so that **ring A** is any six membered cycloalkyl or heterocyclo ring having from 0 to 2 heteroatoms [**note:** but **ring A** is *not* a five-membered cycloalkyl or heterocycle ring];

Q is a bond, -C(=O)- or a branched or straight chain C_{1-4} alkylene optionally substituted with one to two $\mathbf{R_4}$;

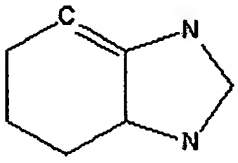
Ar is an optionally-substituted aryl or heteroaryl;

$\mathbf{R_1}$ – $\mathbf{R_{19}}$ are any of the values defined in **Claim 1** (on pp. 58 – 60 of the Specification);

p is 1, 2 or 3; and

q is 1, 2, or 3.

The expanded search thus covered more than 6 different U.S. Patent Classifications and Subclassifications, and encompassed the following eight variations in the bicyclic core structure: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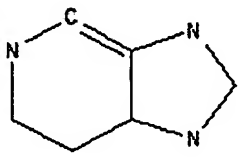
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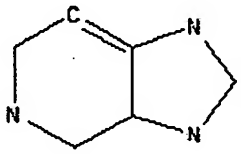
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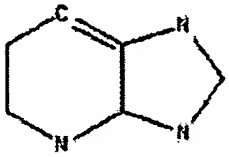
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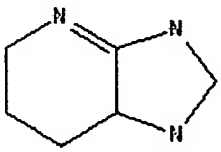
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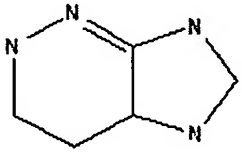
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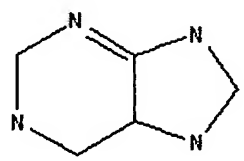
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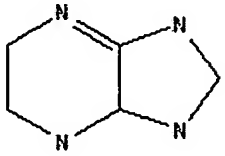
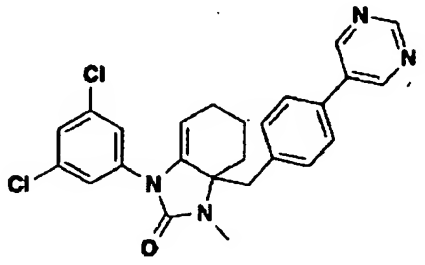
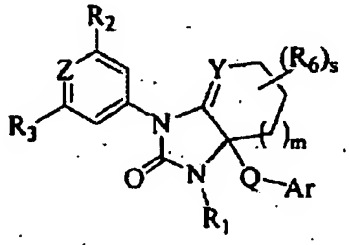

. The expanded search also permitted the aryl attachment to the ring nitrogen at the 1-position of the condensed ring to be phenyl or 4-pyridyl (according to the value for **Z**), and for **Ar** to be a

nitrogen-containing heterocycle, such as the pyrimidinyl-benzyl rings embodied in "Example 12" on page 57 of the Specification,



Compounds in **Claims 2 – 18** were also searched, except for the following: (1) dependent **Claim 3** excluding "J_1 is a bond," (i.e., where ring A is a *five*-membered ring); and (2) **Claim 10**, drawn to compounds of formula (Ia),



, excluding "**m** is 0 [zero]" (i.e., where ring A condensed with the imidazolone ring had to be a *six*-membered ring containing 0 – 2 ring nitrogen atoms – or, in the case of **Claim 10**, containing 0 or 1 ring nitrogen atoms – but could not be a *five*-membered ring). The search was also expanded to encompass the additional variables R_{20} – R_{24}, **n**, **r**, **s**, and **t** defined in **Claim 5** and **Claim 10**.

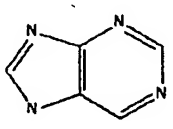
Summary of Disclosure and Journal Data Supporting Use in Claimed Diseases

"LFA-1," is the abbreviation for "Leukocyte Function-associated Antigen-1," which is a cell surface receptor found on leukocytes. "ICAM," is the abbreviation for Intercellular [sometimes "Intracellular"] Adhesion Molecule-1, which is a glycoprotein that is likewise found on cell surfaces of leukocytes, endothelial and epithelial cells, and several other cell types. See Anderson, M. and Siahaan,T., "Targeting ICAM-1/LFA-1 interaction for controlling autoimmune diseases: designing peptide and small molecule inhibitors," Peptides, vol. 24, pages

487 – 501 (2003) at p. 489, col. 2, lines 28 – 44 (LFA-1) and p. 490, col. 2, lines 5 – 15 (ICAM). The interaction of LFA-1 and ICAM is believed to be essential for T cell activation as well as migration of T-cells to target tissues so that, when the LFA-1/ICAM interaction is inhibited, T-cells are prevented from firm adhesion to certain cells and are thus prevented from taking part in the immune response. Anderson, *supra*, at Abstract, lines 2 – 3 and p. 489, col. 1, lines 13 – 16. Another published study of LFA-1/ICAM found that "our *in vivo* studies point to an important role for LFA-1 in trafficking of lymphocytes to peripheral lymph nodes, mesenteric lymph nodes and acute inflammatory sites." Andrew, D., et al., "Transendothelial migration and trafficking of leukocytes in LFA-1-deficient mice," Eur. J. Immunol., vol. 28, pages 1959-1969 (1998) at p. 1959, col. 1, line 2, to col. 2, line 13; p. 1966, col. 2, lines 42-53; and p. 1967, lines 1-2; see also Ding, Z., et al., "Relative Contribution of LFA-1 and Mac-1 to Neutrophil Adhesion and Migration," J. Immunology, vol. 163, pages 5029-5038 (1999) at p. 5037, col. 2, lines 2-21.

The adhesion molecules LFA-1 and ICAM-1 have been studied in the medical conditions claimed in **Claim 19** and **Claim 20**, as amended, including *in vitro* data demonstrating increased activity of LFA-1 and ICAM in active forms of the disease, and, in some cases, *in vivo* data from animal models or early-phase human clinical trials using chemical compounds or monoclonal antibodies which inhibit LFA-1/ICAM activity as methods of treatment. See, e.g., Anderson, *supra*, at p. 492, col. 1, lines 40 et seq. (overview of clinical studies of antibodies inhibiting LFA-1/ICAM); p. 492, col. 2, lines 31 et seq. (peptides and small molecules inhibiting LFA-1/ICAM); and p. 493, Table 1 (clinical studies of T-cell activation modulators for treatment of psoriasis, transplantation rejection, diabetes, rheumatoid arthritis, hypersensitivity, and immunosuppression); see also, Dedrick, R., et al., "Adhesion molecules as therapeutic targets for

autoimmune diseases and transplant rejection," Expert Opin. Biol. Ther., vol. 3(1), pages 85-95 (2003) at p. 87, col. 1, lines 1–4 ("adhesion molecule expression is elevated in many chronic autoimmune states, including rheumatoid arthritis, psoriasis, and multiple sclerosis"). The dosing and safety profile of certain LFA-1 or ICAM-1 inhibitors was known in the art from such studies. See, e.g., Glover, J., "Phase I Safety and Pharmacokinetic Profile of an Intercellular Adhesion Molecule-1 Antisense Oligodeoxynucleotide (ISIS 2302)," J. Pharm. Exp. Ther., vol. 282(3), pages 1173-1180 (1997) at p. 1173, col. 2, lines 1-13; p. 1180, lines 1-4.

Specifically, one contemporary journal publication stated that "the expression of ICAM-1 and VCAM-1 play an important role in allograft rejection and many autoimmune diseases such as RA, MS, Graves, Crohn's, AIDS, diabetes, graft-versus-host disease (GVHD) and inflammatory bowel disease." Yusuf-Makagiansar, H. et al, "Inhibition of LFA-1/ICAM-1 and VLA-4/VCAM-1 as a Therapeutic Approach to Inflammation and Autoimmune Diseases," Medicinal Research Reviews, vol. 22(2), pages 146-167 (2002) at p. 151, lines 29-48; and p. 152, lines 11-14. Monoclonal antibodies which inhibited LFA-1 were studied in non-human primates and improved survival of allogenic cardiac transplantation grafts. Poston, R., et al., "Effects of Humanized Monoclonal Antibody to Rhesus CD11a in Rhesus Monkey Cardiac Allograft Recipients," Transplantation, vol. 69(10), pages 2005-2013 (May 2000) at p. 2012, col. 1, lines 14-29; see also Malm, H., et al., "CTLA4IG Induces Long-Term Graft Survival of Allogenic Skin Grafts and Totally Inhibits T-Cell Proliferation in LFA-1-Deficient Mice," Transplantation, vol. 73(2), pages 293-297 (Jan. 2002) at p. 297, lines 9-12. In addition, chemical compounds having a "purine" core,  , which were substituted by a five-

membered ring at the 1-position (similar to embodiments of the present invention) were patented for use as treatment of allograft rejection after transplantation. See, e.g., U.S. Patent 6,436,947 at col. 22, lines 6 – 16.

Dedrick, *supra*, reviewed studies of LFA-1 and ICAM inhibitors in transplant rejection, rheumatoid arthritis, psoriasis, and Crohn's disease. See, e.g., Dedrick, *supra*, at p. 88, lines 15 et seq. (animal model studies for transplantation of heart allografts), p. 89, col. 1, lines 16 et seq. (studies with monoclonal antibodies to "CD11a" for psoriasis), p. 89, col. 2, lines 30 et seq. (animal model studies with ICAM-1 inhibitor monoclonal antibodies for arthritis and transplants, and human trials for renal transplantation and RA); and p. 90, col. 1, lines 18 – 41 (preliminary clinical trials of an antisense oligonucleotide to ICAM-1 for Crohn's disease).

The Specification in this application disclosed twenty-three patent application publications using other chemical compounds used to modulate LFA-1/ICAM which claimed use as anti-inflammatory agents. See Specification at p. 3, line 20 to p. 4, line 7 (disclosing thiadiazole, benzylamine, bromotryptophan, imidazolidine, and hydantoin derivatives as anti-inflammatory agents).

ICAM-1 was also known in the art to have a role in the pathogenesis of Multiple Sclerosis, probably by assisting the migration of inflammatory T-lymphocytes through the compromised blood-brain barrier of those persons with disease. See, e.g., Dietrich, J., "The adhesion molecule ICAM-1 and its regulation in relation with the blood-brain barrier," J. Neuroimmunology, vol. 128, pages 58-68 (2002) at pages 62, col. 2, lines 29 - 38. Chemical compounds having a "purine"-type ring core, and substituted by a five-membered ring at the 1-position (similar to the present invention), were disclosed as suppressors of T-cells, and having

use for the treatment of multiple sclerosis. U.S. Patent 6,436,947 at col. 23, line 37-40; see also U.S. Patent 3,930,005 at col. 2, lines 43-44.

The overexpression of ICAM-1 in Systemic Lupus Erythematosus (SLE) has been shown in a murine model to correlate well with disease activity (i.e., an increase in ICAM levels correlated with increased disease activity). Zameer, A. and Hoffman, S., "Increased ICAM-1 and VCAM-1 expression in the brains of autoimmune mice," J. Neuroimmunology, vol. 142, pages 67-74 (2003) at p. 72, col. 2, line 55 to p. 73, col. 1, line 10. Another study involving drug-induced lupus found that "our results indicate that altered LFA-1 expression...could also contribute to the pathogenesis of idiopathic human lupus." Yung, R., "Mechanisms of Drug-Induced Lupus II. T Cells Overexpressing Lymphocyte Function-associated Antigen 1 Become Autoreactive and Cause a Lupuslike Disease in Syngeneic Mice," J. Clin. Invest., vol. 97, pages 2866-2871 (1996) at p. 2871, lines 6-8. LFA-1 inhibitors have been proposed for treatment of SLE patients, even while some of the clinicians conducting the studies acknowledge that, in the majority of clinical studies so far, little benefit to patients has been reported. Kevil, C. et al., "Loss of LFA-1, but not Mac-1, Protects MRL/MpJ-Fas Mice from Autoimmune Disease," Am. J. Pathol., vol. 165, pages 609-616 (2004) at p. 615, col. 2, lines 25-35 and lines 14 – 21. As before, chemical compounds with a "purine"-type core structure (similar to the present invention) were disclosed to be useful in the treatment of Systemic Lupus Erythematosus. See, e.g., U.S. Patent 6,436,947 at col. 22, line 57 – 62.

One of the earliest disease models in which LFA-1/ICAM interactions were studied was Rheumatoid Arthritis (RA). See Yokota, A., et al., "High Avidity State of Leukocyte Function Associated Antigen-1 on Rheumatoid Synovial Fluid T Lymphocytes," J. Immun., vol. 55, pages

4118-4124 (1995) at p. 4118, col. 2, lines 25-34; p. 4123, lines 55-59 ("our data showing the...high avidity state of LFA-1 specific for RA implicates LFA-1 as one of the central molecules in the onset and the maintenance of RA"); see also Anderson, *supra*, at p. 493, Table 1 (summarizing three studies of molecules which are T-cell modulators for treatment of RA patients). Chemical compounds with a "purine"-type core structure, substituted with a five-membered ring at the 1-position, were known in the art also to be useful for treatment of rheumatoid arthritis. See U.S. Patent 6,436,947, at col. 23, lines 45–52 and col. 24, lines, 45 – 52; and U.S. Patent 3,930,005, at col. 2, lines 31-33.

The role of LFA-1/ICAM-1 in osteoarthritis (OA) has not been as well-studied as in rheumatoid arthritis; even so, at the time of this application it was known in the art that ICAM-1 was expressed at the surface of human osteoblast cells recovered from OA patients. See Tanaka, Y., et al., "Intercellular Adhesion Molecule 1 Discriminates Functionally Different Populations of Human Osteoblasts," J. Bone & Mineral Research, vol. 15(10), pages 1912-1923 (Oct. 2000), at p. 1922. Another study demonstrated that LFA-1/ICAM-1 interactions play an important role in osteoclast development. Tani-Ishii, N., et al., "The role of LFA-1 in osteoclast development induced by co-cultures of mouse bone marrow cells and MC3T3-G2/PA6 cells," J. Periodontal Research, vol. 37, pages 184-191 (2002) at p. 188, col. 3, lines 5 - 10 and Fig. 3. A recent review article discussed the role of ICAM-1 in the pathogenesis of OA and as a potential target for treatment. Lavigne, P., at al., "Involvement of ICAM-1 in bone metabolism: a potential target in the treatment of bone diseases?" Expert Opin. Biol. Ther., vol. 5(3), pages 313–320 (March 2005) at p. 315, col. 1, lines 43–45 and col. 2, lines 4–7, 30–33 ("ICAM-1 is also

involved in the pathophysiology of OA ... ICAM-1 has been reported in OA tissues and implicated in the mediation of inflammation and apoptosis").

Inflammatory lung injury, such as chronic obstructive pulmonary disease (COPD) was likewise known in the art to be linked to greater activity of adhesion molecules, including LFA-1/ICAM. See, e.g., Mulligan, M., et al., "Role of β1, β2 Integrins and ICAM-1 in Lung Injury after Deposition of IgG and IgA Immune Complexes," J. Immunology, vol. 150(6), pages 2407 – 2417 (March 1993), at p. 2414, col. 2, lines 6 – 10, et seq.; see also Mulligan, M., et al., "Compartmentalized Roles for Leukocytic Adhesion Molecules in Lung Inflammatory Injury," J. Immunology, vol. 154, pages 1350-1363 (1995) at p. 1351, col. 1, lines 7-15; p. 1362, col. 1, lines 3-26. Recruitment and activation of neutrophils is an important step in the pathogenesis of COPD, and expression of adhesion molecules, such as LFA-1 and ICAM-1, was known to be important in this process. Noguera, A., et al., "Expression of Adhesion Molecules and G Proteins in Circulating Neutrophils in Chronic Obstructive Pulmonary Disease," Am. J. Respir. Crit. Care Med., vol. 158, pages 1664-1668 (1998) at p. 1664, col. 1, lines 1-10. In one study conducted to clarify the reasons why some cigarette smokers develop COPD and others do not, the authors concluded that one reason was greater release of ICAM-1 in cigarette smokers with COPD than in those without COPD. Rusznak, C., et al., "Effect of Cigarette Smoke on the Permeability and IL-1-Beta and sICAM-1 Release from Cultured Human Bronchial Epithelial Cells," Am. J. Respir. Cell Mol. Biol., vol. 23, pages 530-536 (2000) at page 534, col. 1, lines 30 – 32; and p. 535, col. 2, lines 12 – 25; see also Takabatake, N., et al., "Impaired systemic cell-mediated immunity and increased susceptibility to acute respiratory tract infections in patients with COPD," Respiratory Medicine, vol. 99, pages 485-492 (2005) at p. 489, col. 2, lines 46-50.

Likewise, the mechanism of airway obstruction of acute severe asthma was established in the art to involve neutrophilic infiltration of airways. See Agusti, C., et al., "Goblet Cell Degranulation after Antigen Challenge in Sensitized Guinea Pigs," Am. J. Respir. Crit. Care Med., vol. 156, pages 1253-1258 (1998) at p. 1253, col. 1, lines 1-9; p. 1257, col. 1, lines 1-7. Pretreatment with a blocking antibody to ICAM-1 prevented both neutrophilic recruitment, goblet cell degranulation and mucus obstruction, which are characteristic of acute asthma attacks. Id. at 1257, col. 1, lines 1 – 7 and col. 2, lines 19 – 27.

Intestinal diseases with an inflammatory component, such as Crohn's disease and inflammatory bowel disease, had been known in the art to be linked with adhesion molecules which assisted with migration of neutrophils. See Jaye, D. and Parkos, C., "Neutrophil Migration across Intestinal Epithelium," Annals of the New York Academy of Sciences, vol. 915, pages 151-161 (2000) at p. 151, lines 2 – 4; p.156, lines 9 – 23. A double blind placebo-controlled study of an investigational ICAM-1 antisense oligodeoxynucleotide, alicaforsen, was conducted in early phase clinical trials in patients with steroid-dependent Crohn's disease, although the overall efficacy results were equivocal because the dose given was hypothesized by the study's authors to be too low. Yacyshyn, B., et al., "Double blind, placebo controlled trial of the remission and steroid sparing properties of an ICAM-1 antisense oligodeoxynucleotide, alicaforsen, in active steroid dependent Crohn's disease," Gut, vol. 51, pages 30 – 36 (2002) at p. 34, col. 2, lines 2 – 18; and p. 35, lines 10 – 18 and lines 29 – 39; see also Bernstein, C., "The potential for the β2 integrin-ICAM-1 adhesion paradigm as a therapeutic target in Crohn's disease," Current Opinions in Anti-Inflammatory & Immunomodulatory Invest. Drugs, vol. 1(4),

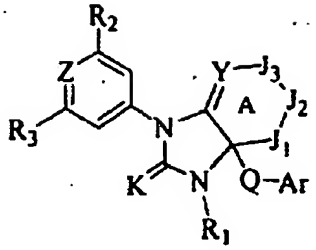
pages 308-315 (1999) at p. 311, lines 48-59 (summarizing the results from the early-phase clinical trials of investigational antisense ICAM-1 inhibitor "ISIS-2302" for Crohn's disease).

At the time of this application, Type I (insulin dependent) diabetes was generally accepted in the art to be a cellular-mediated autoimmune disease. Mysliwiec, J., et al., "CD11a Expression and soluble ICAM-1 levels in peripheral blood in high-risk and overt type 1 diabetes subjects," Immun. Letters, vol. 70, pages 69 – 72 (1999) at p. 69, col. 1, lines 6 – 8. That same study suggested that LFA-1 and sCAM-1 [soluble ICAM-1] "play an important role in the pathogenesis of type I diabetes." Id. at p. 71, col. 2, lines 39 – 41. And, as noted for other cellular-mediated autoimmune diseases, U.S. Patent 6,436,947 discloses purine compounds (similar in structure to the compounds in the present invention) which are useful in the treatment of insulin-dependent diabetes mellitus. U.S. Patent 6,436,947 at col. 22, lines 17 – 23.

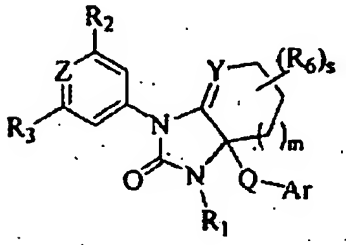
The Specification discloses two separate assay processes ("H1-HeLa Adhesion" and "HUVEC adhesion") which were used to measure the level of activity of these compounds as inhibitors of LFA-1/ICAM (Specification at p. 40, lines 10 – 30 and p. 41, lines 4 – 30) and the Specification states that the test compounds showed a "measurable level of activity" as inhibitors of LFA-1 and/or ICAM-1 (Specification at p. 40, line 9).

Examiner's Amendment to Claims

After the "expanded" searches of the prior art described above, the examiner communicated to applicant, Laurelee Duncan, on April 6, 2005, that the initial restriction was being withdrawn, and that **Claims 19 and 20** would be rejoined for purposes of examination, commensurate with the scope of the allowable products of the invention. During telephone conversations on April 6, 7, 8, 12, 13, 14 and 15, 2005, the examiner and applicant discussed the



scope of compounds of formula (I) and (Ia)



which had been searched and which appeared to be free of the art, as well as the disclosure in the Specification and scientific journal references supporting methods of using the allowable compounds of formula (I) to treat particular LFA-1/ICAM-associated conditions. Applicant cancelled several of the medical conditions listed in the original **Claims 19 and 20**, but stated that, in so doing, did not waive or disavow rights to pursue claims for these conditions in a subsequent application, such as a Continuation or Divisional application.

Based upon these communications, the following Examiner's Amendment was agreed to by the Examiner and Applicant on April 15, 2005.

In the original Claims:

In **Claim 1**, page 58, line 13, delete "a bond," after J_1 is.

In **Claim 1**, page 58, line 17, delete "five-to-" before six membered cycloalkyl.

In **Claim 3**, page 61, line 5, delete "a bond or" after J_1 is.

In **Claim 10**, page 65, line3, delete "0 or" after *m* is.

In **Claim 19**, page 66, line 20, delete "of inhibiting an" and insert ---of treating a---.

In **Claim 19**, page 66, line 22, delete "." after claim 1, and insert ---wherein the LFA-1/ICAM-associated condition is selected from acute or chronic graft-versus-host reactions, acute or chronic transplant rejection, multiple sclerosis, rheumatoid arthritis, osteoarthritis, diabetes, inflammatory bowel disease, Crohn's disease, reperfusion injury, psoriasis, asthma, chronic obstructive pulmonary disease (COPD), and systemic lupus erythematosus.---.

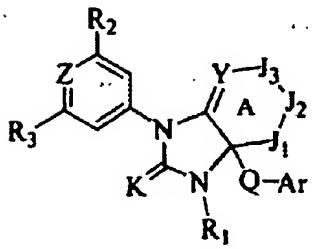
In **Claim 20**, page 67, lines 1 – 16, delete "The method of claim 19 in which LFA-1/ICAM-associated condition is selected from acute or chronic graft vs. host reactions, acute or chronic transplant rejection, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, osteoporosis, diabetes, cystic fibrosis, inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, ulcerative colitis, Alzheimer's disease, shock, ankylosing spondylitis, gastritis, conjunctivitis, pancreatis, multiple organ injury syndrome, myocardial infarction, atherosclerosis, stroke, reperfusion injury, acute glomerulonephritis, vasculitis, thermal injury, necrotizing enterocolitis, granulocyte transfusion associated syndrome, Sjogren's syndrome, eczema, atopic dermatitis, contact dermatitis, urticaria, schleroderma, psoriasis, asthma, pulmonary fibrosis, allergic rhinitis, oxygen toxicity, emphysema, chronic bronchitis, acute respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), hepatitis B, hepatitis C, organ-tissue autoimmune disease, autoimmune thyroiditis, uveitis, systemic lupus erythematosus, Addison's disease, autoimmune polyglandular disease, and Grave's disease" and insert ---The method of claim 19 in which the LFA-1/

ICAM-associated condition is selected from acute or chronic graft versus host reactions, acute or chronic transplant rejection, rheumatoid arthritis, psoriasis and chronic obstructive pulmonary disease---.

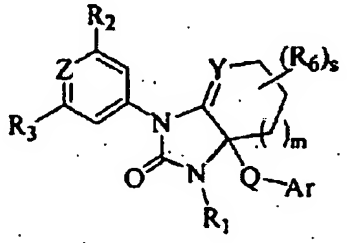
These amendments are also recorded on the Summary of Telephone Interview Form PTO-413, dated April 15, 2005.

Reasons for Allowance

The present invention is directed to chemical compounds of formula (I)



and formula (Ia)



, wherein:

K is O or S;

Z is N or C($\mathbf{R^8}$);

Y is N or C($\mathbf{R^8}$);

$\mathbf{J_1}$ is N($\mathbf{R_5}$) or -C($\mathbf{R_{6a}R_{7a}}$)- [**note:** but $\mathbf{J_1}$ is *not* a bond];

$\mathbf{J_2}$ is N($\mathbf{R_5}$) or -C($\mathbf{R_{6b}R_{7b}}$)-;

$\mathbf{J_3}$ is N($\mathbf{R_5}$) or -C($\mathbf{R_{6c}R_{7c}}$)-; and only one of $\mathbf{J_1}$, $\mathbf{J_2}$ and $\mathbf{J_3}$ may be $\mathbf{NR_5}$ so that **ring A** is any six membered cycloalkyl or heterocyclo ring having from 0 to 2 heteroatoms [**note:** but **ring A** is *not* a five-membered cycloalkyl or heterocycle ring];

Q is a bond, -C(=O)- or a branched or straight chain C_{1-4} alkylene optionally substituted with one to two $\mathbf{R_4}$;

Ar is an optionally-substituted aryl or heteroaryl;

$R_1 - R_{24}$ are any of the values defined in **Claim 1** (on pp. 58 – 60 of the Specification), **Claim 5** (on page 62, lines 6 – 21 of the Specification) or **Claim 10** (on pages 63 – 65 of the Specification);

p and **q** are independently 1, 2, or 3;

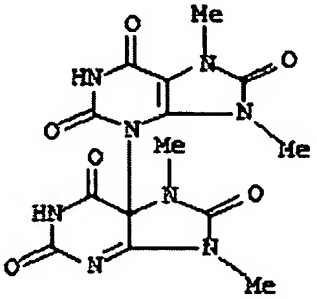
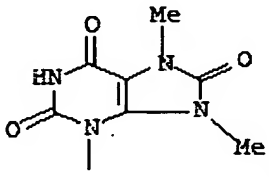
m is 1;

n is 0, 1 or 2;

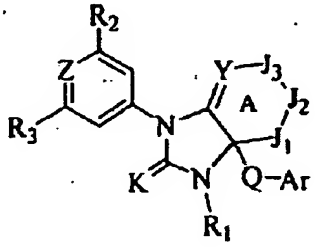
r and **s** are 0, 1, 2, 3, or 4;

t is 0, 1 or 2.

their pharmaceutical compositions, pharmaceutically-acceptable salts, hydrates, prodrugs or enantiomers, and their claimed uses as methods of treatment, *inter alia*, as LFA-1/ICAM inhibitors for treatment of selected inflammatory or autoimmune conditions in mammals.

The closest prior art of record was disclosed in Subramanian, P. and Dryhurst, G., "Isolation and characterization of 5-[3'-(7',9'-dimethyluric acid)]-7,9-dimethyl-$\Delta^{3,4}$-isouric acid," J. Electroanalytical Chem., vol. 262(1-2), pages 281-287 (April 1989) which disclosed the title compound:  (Subramanian at Abstract; at p. 285, line 12; and at p. 286, line 16 ["compound 3" in Scheme 1]). The corresponds to the present invention of formula (I) wherein: **K** is O; **Y** is N; **Q** is a bond; **Ar** is  attached at the "3a" position

of the condensed bicyclic ring; **Z** is N or C(R^8); J_1 is -C($R_{6a}R_{7a}$)- where R_{6a} and R_{7a} are taken together to form a keto group (=O); J_2 is N(R_5) where R_5 is hydrogen; J_3 is -C($R_{6c}R_{7c}$)- where R_{6c} and R_{7c} are taken together to form a keto group (=O); R_1 is methyl; ***but*** the requisite phenyl (or pyridyl) ring [containing variable **Z**] attached to the bicyclic ring nitrogen is, instead, a "methyl" group in the prior art and thus does not anticipate or render obvious the present invention. In addition, the variable **Ar** in the prior art is not an aromatic ring (although it is a heterocyclic ring), and does not meet that limitation of the present invention.

Although there are numerous prior references which are structurally similar to formula (I) of the present invention, 

, three characteristics of the present invention which distinguish it from the prior art searched: **(1)** the substituent **–Q–Ar** attached to the "3a" position of the condensed ring, with **Ar** required to be "aryl or heteroaryl"; **(2)** the double bond in ring A between positions "7a" and "7" in the otherwise saturated condensed **ring A**; and **(3)** the phenyl (or 4-pyridyl) substituent attached to the ring nitrogen atom at the "1-position" of the condensed ring.

The "method of use" claims, **Claim 19** and **Claim 20 (as amended)**, were supported by the disclosure in the Specification and/or published studies in the scientific literature for LFA-1/ICAM-associated conditions (as described above); and, therefore, **Claim 19** and **Claim 20, as amended**, are allowable.

Conclusion

Claims 1 – 20, as amended by the Examiner's Amendment above, are free of the prior art of record, and are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Anthony J. Paviglianiti** whose telephone number is **(571) 272-3107**. The examiner can normally be reached on Monday-Friday, 8:30 a.m. - 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, can be reached at (571) 272-0699. **The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300. Please note that this is a new central FAX number for all official correspondence.**

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